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54 Pharmaceutical preparation containing metformin and method for producing it

57 The present invention relates to pharmaceutical compositions containing metformin as an active substance and a hydrocolloid-forming agent as a retardant, and, optionally, standard pharmaceutical auxiliary substances, the residual moisture content in the pharmaceutical composition being 0.5–3% by weight.

The invention further relates to a method for the manufacture of pharmaceutical compositions containing metformin as an active substance and a hydrocolloid-forming agent as a retardant, and, optionally, additional standard pharmaceutical auxiliary substances, characterized in that the active substance and retardant, or a portion thereof, are granulated with an aqueous solvent optionally containing a binder, and the remaining portion of the retardant or other standard pharmaceutical auxiliary substances is optionally mixed with the granulate, which is then dried until the residual moisture content is 0.5–3% by weight.

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## Description

The invention relates to pharmaceutical preparations containing metformin hydrochloride (also referred to hereinafter as metformin) as an active substance and a hydrocolloid-forming agent as a retardant, and to a method for producing it.

It is known that metformin hydrochloride is a biguanide derivative (1,1-dimethylbiguanide monohydrochloride) which acts as an oral antidiabetic. Metformin delayed-release tablets are marketed containing 850 mg metformin hydrochloride per film tablet (Glucophage® retard). Since metformin, in contrast to other active substances, cannot be pressed in its pure form (the substance disintegrates in an unchanged form after compression), framework-forming auxiliary substances such as polyvinyl acetate were used in these high-dose delayed-release tablets as a retardant (Lipha, Glucophage® technical information, August 1991, "Bundesverband der Pharmazeutischen Industrie e.V." [German Association of Pharmaceutical Industries], published by Rote Liste 1993, Edition Cantor, Aulendorf 1993). The mechanism of action of such framework tablets is based on the fact that the readily water-soluble metformin diffuses from the tablet independently of the pH in the gastrointestinal tract, whereas the tablet framework with the coating is excreted essentially unchanged.

The disadvantage of using such framework-forming auxiliary substances such as polyvinyl acetate, however, is that said auxiliary substances must be processed with organic solvents in particular during the granulation process, and the organic solvent must be removed again as much as possible before the granulate is further processed into compressed pharmaceutical forms of administration and pressed into tablets, for example.

The object of the invention is to provide a pharmaceutical composition in the form of a well-compressed granulate which contains the active substance metformin with a highest possible active substance content and a retardant which causes a controlled release of the active substance. However, the pharmaceutical composition should not contain framework formers which must be processed with organic solvents, but instead should have a composition based on substances that can be processed aqueously. These pharmaceutical compositions should be readily compressible so that they are suitable for the manufacture of solid pharmaceutical forms of administration such as, for example, tablets, dragees, or compacted products for filling into capsules. In the manufacture of tablets or other compacted products, the maximum total weight should be approximately 1200–1300 mg in order not to jeopardize the therapeutic safety (patient compliance), since larger oral forms of administration often are not taken regularly as prescribed.

A further object in the processing of the granulate for these high-dose forms of administration, particularly in the manufacture of tablets, is to solve the problem of capping caused by the active substance, which is particularly pronounced in the case of metformin, in order to avoid losses of yield during production and to avoid impairment of the pharmaceutical quality. Capping refers to the detachment of compressed substances in layers from the manufactured pellet during pressing or shortly afterwards (Schepky G. in: Bruchhausen, F. von et al.; publishers; Hagers Handbuch der pharmazeutischen Praxis [Handbook of Pharmaceutical Practice], Volume 2, Methoden [Methods], 5th ed., Springer Press, Berlin 1991). In the case of metformin, especially when high doses of active substance are present in the granulate, it has been found that the tendency toward capping is particularly high during the production of tablets.

The causes of these tableting problems can be diverse and complex. Capping can be caused by insufficient action of the binding agent, an inadequate or excessive moisture content of the granulate, unsuitable crystal forms, strongly aerophilic substances, excessive porosity, excessive proportion of powder, excessive interparticulate binding between the granulate particles, and by unsuitable granulate forms. Machine-related factors such as excessive pressing force, improperly used or worn tools, excessive pressing rates, and poor deaeration of the matrix (fixed pressure) can result in capping. In the case of the active substance metformin, however, it has been shown that the usual measures are not sufficient to satisfactorily control the capping of the tableting mass. A relatively high proportion of defective tablets was regularly found during tablet production, and the tableting had to be discontinued due to high reject rates.

In the present case, the object of the invention is achieved by providing high-dose pharmaceutical compositions containing metformin which contain a hydrocolloid-forming agent as a retardant and which have a residual moisture content of 0.5–3% by weight in the pharmaceutical composition. These pharmaceutical compositions can be advantageously manufactured using aqueous solvents, so that organic solvents are no longer required. In addition, these compositions are surprisingly easy to compress. They are therefore particularly suitable for the manufacture of solid pharmaceutical forms of administration such as tablets, dragees, or capsules, for example, and these can be manufactured using conventional processing machines on a commercial scale and in a good quality as well as in a high yield without large losses due to the undesired capping. Thus, an additional subject matter of the invention is a corresponding method for manufacturing these solid forms of administration by using the appropriate pharmaceutical compositions according to the invention in the form of granulates having a residual moisture content of 0.5–3% by weight. The residual moisture content is preferably 1–2.5% by weight, in particular 1.5–2% by weight.

Surprisingly, it was also found that in the case of the granulate according to the invention it is possible to omit the addition of humectants which are otherwise often necessary to set a constant residual moisture content until the granulate is compressed. This is particularly advantageous because the addition of auxiliary substances may be minimized, and pharmaceutical compositions are obtained with a relatively high content of active substance. In addition, these compositions have the advantage that they are stable under storage, with regard to the moisture content, for a period of two days or more (starting from the production up to the use of the granulate for tableting) before they are compressed without a disadvantageous change in the

composition being detectable. This is advantageous since it enables several partial batches of production lots of the pharmaceutical composition to be produced, and at a later time these can then be mixed as a mass ready to be pressed in a common last process step and can be processed to solid pharmaceutical forms of administration. In addition, it was unexpectedly found that the use of a hydrocolloid-forming agent in particular enabled for the first time the known poor compressibility of metformin to be brought under control in a technically satisfactory manner. In addition, the approach according to the invention enables the desired retardation and compressibility to be ensured by the choice of the hydrocolloid-forming agent as the retardant and with a suitable control of the production process (observing the critical residual moisture content of 0.5–3% by weight), although the proportion of the hydrocolloid-forming agent in the formulation composition is unusually low. This is even more surprising since the major proportion of the formulation (about 70–95% by weight) is formed by the active substance, whose water-absorbing capacity is very small (the pure active substance binds only 0.04% by weight water at a relative moisture content of 90%).

The proportion by weight of the active substance in the high-dose pharmaceutical composition is in the range of at least 70% by weight, preferably 80–95% by weight, relative to the pharmaceutical composition. The active substance can be used in the form of acid addition salts of inorganic or organic acids such as hydrochloric acid, formic acid, acetic acid, malic acid, tartaric acid, or fumaric acid, for example. The hydrochloride salt is preferably used.

The proportion of hydrocolloid-forming agent in the pharmaceutical composition is up to 15% by weight, preferably 4–10% by weight and in particular approximately 6–8% by weight.

Within the sense of the invention, the customary hydrophilic gel-forming agents are suitable as hydrocolloid-forming agents or as hydrophilic swelling substances such as for example cellulose derivatives, dextrans, starch, carbohydrate-based polymers, natural and hydrophilic gums, xanthanes, alginates, gelatin, polyacrylic acid, polyvinyl alcohol, or polyvinylpyrrolidone. In the case of the cellulose derivatives, the alkyl or hydroxyalkyl cellulose derivatives preferably come into consideration, such as methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, methylhydroxyethyl cellulose, methylhydroxypropyl cellulose, or sodium carboxymethyl cellulose, for example. In a preferred embodiment variant of the invention, methylhydroxypropyl cellulose (MHPC) is used. The hydrocolloid-forming agents can be used individually as well as in mixtures of two or several colloid-forming agents. The standard polymers suitable for pharmaceutical purposes with various degrees of substitution and/or different molecular weights corresponding to a different degree of viscosity of the aqueous solution can be used as suitable cellulose-based polymeric colloid-forming agents.

The use of hydrocolloid-forming agents as retardants is based on the property of the hydrocolloid-forming agents, when they are contacted with a release medium or digestive juices, to swell and form a gel matrix which erodes to release the active substance. The interaction between the amount of hydrocolloid-forming agent and the degree of viscosity determines the time course of the release. Thus, for example, a high proportion (70–95% relative to the core weight of a tablet) of polyvinyl alcohol having a low or average viscosity level can retard riboflavin for several hours (Möckel J. E., Lippold B. C., Pharm. Research, 1993, 10, 1066–1070).

The compressed forms of administration produced using the pharmaceutical composition according to the invention, such as for example metformin delayed-release tablet cores, can be additionally provided with a film envelope. The film envelope on the one hand can cause an additional retardation by using those film materials which represent a film-forming agent which is usually suitable for these purposes. On the other hand, the film envelope used can be a taste-neutralizing film-forming agent to which dyes can optionally be added. In addition, it is also possible, for example, to use films that are resistant to gastric juices. The proportion by weight of the film envelope relative to the final tablet is in the usual range of 0.3–3.0% by weight, preferably 0.8–1.2% by weight. Film-forming agents, such as for example ethyl cellulose, poly(methyl methacrylate) derivatives (Eudragit®), and also soluble cellulose derivatives such as methylhydroxypropyl cellulose and cellulose derivatives for forming films resistant to gastric juices such as cellulose acetate phthalate or methylhydroxypropyl cellulose phthalate, come into consideration as film-forming agents. Ethyl cellulose is preferably used. The dissolution of the active substance can be delayed by the film that is formed. Softeners, pore formers, and pigments may be present in the film envelope as standard auxiliary substances.

The pharmaceutical forms of administration according to the invention such as tablets, for example, contain—in addition to the active substance whose proportion in the form of administration can be in the range of 70–95% by weight (for example, 850 mg of the active substance is preferably used in the case of delayed-release tablets) and the retardant—preferably 2–10% by weight binder, up to 2% by weight, preferably 0.1–0.3% by weight flow-regulating agent, and up to 2% by weight, preferably 0.4–1.1% by weight lubricant, each relative to the total weight of the material ready to be tableted or of the tablet core. Flow-regulating agents which come into consideration for the tablet according to the invention are standard agents such as colloidal silicon dioxide, for example. Talcum or stearic acid or the alkali or alkaline earth salts thereof, in particular magnesium stearate, are examples of suitable lubricants. Examples of binding agents that can be used are cellulose derivatives, in particular alkyl and hydroxyalkyl celluloses, especially methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, methylhydroxyethyl cellulose, methylhydroxypropyl cellulose, and sodium carboxymethyl cellulose, among others, dextrans, starches, especially soluble starches, other carbohydrate-based polymers such as for example galactomannans, natural gums such as gum arabic, tragacanth, Sterculia, Acacia, and others, xanthane, alginates, polyacrylic acid, polyvinyl alcohol, and polyvinylpyrrolidone. Polyvinylpyrrolidone is preferably used.

The pharmaceutical forms of administration according to the invention such as tablets, for example, are produced by

dry-mixing the active substance, the retardant or a portion of the retardant, and, optionally, additional auxiliary substances, wet-granulating with water or an aqueous solution of a binder, drying the material ready for tableting to a desired residual moisture content, and, optionally, subsequently mixing the remaining portion of the retardant or additional pharmaceutical auxiliary substances with the granulate, so that in the last process step a residual moisture content of 0.5–3% by weight is achieved in the pharmaceutical composition. In the wet granulation a portion of the active substance, the auxiliary substances used, as well as the retardant may also be present completely or partially dissolved or suspended in water. Organic solvents that are miscible with water, such as for example acetone, or lower alcohols such as methanol or ethanol may optionally be added.

It is practical to adjust the residual moisture content while drying in a fluid bed process in which the moist granulate is dried until the measured moisture content in the exhaust air has reached the value previously determined when the residual moisture content in the drying material was calibrated. The composition thus produced is then processed in the customary manner to form pharmaceutical forms of administration and, for example, is pressed into tablets. The tablets can be coated with a film using standard coating methods. It was found that the residual moisture content of 0.5–3% by weight, which was set using the hydrocolloid-forming agent, ensures that the material ready for tableting can be compressed over the entire range of pressing force required to produce large tablets without capping.

The active substance can be processed completely or partially with the hydrocolloid-forming agent used for retardation to form a granulate, or the hydrocolloid-forming agent is mixed completely with a granulate free of hydrocolloid-forming agent after its production. However, an additional improvement in the tablet-forming properties is achieved when the hydrocolloid-forming agent or a portion thereof is granulated with the active substance.

The tablet is coated by customary methods such as the coating pan or fluid bed process, for example.

The delayed-release tablets according to the invention release metformin in a controlled manner over a period of 0.5–10 hours, preferably over 4 hours (Figure 1). The maximum weight of the tablets is 1200 mg, preferably less than 1000 mg, since due to the use of a hydrocolloid-forming agent large amounts of additional auxiliary substances and in particular humectants, such as for example glycerine or sorbitol, are not necessary.

The invention is explained below, using exemplary embodiments, without being limited to same.

In Examples 1–6 which follow, the residual moisture content was adjusted to a range between 1.95% and 2.80% by weight before the pharmaceutical composition in the form of a mass ready for pressing was compressed into tablets.

#### Example 1

Hydrocolloid-forming agent: methylhydroxypropyl cellulose (MHPC). The MHPC content can be varied from 40 to 95 mg, for example.

Residual moisture: 2.1%.

<u>Components</u>	<u>Tablet (mg)</u>	<u>Mass ready for tablet pressing (kg/1 million pieces)</u>
Core:		
Metformin hydrochloride	850.00	850.00
Methylhydroxypropyl cellulose	60.00	60.00
Polyvidone	38.00	38.00
Magnesium stearate	<u>5.00</u>	<u>5.00</u>
Core total:	953.00	953.00
Film envelope:		
Methylhydroxypropyl cellulose	20.00	20.00
Ethyl cellulose	12.00	12.00
Macrogol	4.00	4.00
Titanium dioxide	<u>4.00</u>	<u>4.00</u>
Envelope total:	40.00	40.00
Film tablet total:	993.00	993.00

#### Production

The production of granulate for a quantity of approximately 1 million tablets was carried out in five partial batches. For each of the five partial batches, 170 kg metformin hydrochloride and 12 kg methylhydroxypropyl cellulose were dry-mixed together and wet-granulated in a mixer with a 10% aqueous binder solution of polyvidone. The granulate was then dried in a fluid bed granulator until it had a sufficient residual moisture content. The five partial batches were combined and mixed with 5 kg magnesium stearate. The mass ready for pressing was tabletted. The tablet cores were coated in a coating pan with the film of the described composition.

The residual moisture content was adjusted to 2.1% in the stated formulation. The tableting proceeded in a corresponding manner without problems; that is, capping of the manufactured tablet mass could not be detected.

#### Example 2

Hydrocolloid-forming agent: hydroxyethyl cellulose  
Residual moisture: 2.0%.

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<u>Components</u>	Tablet (mg)	Mass ready for tablet pressing (kg/1 million pieces)
Core:		
Metformin hydrochloride	850.00	850.00
Hydroxyethyl cellulose	70.00	70.00
Polyvidone	40.00	40.00
Magnesium stearate	<u>5.00</u>	<u>5.00</u>
Core total:	965.00	965.00
Film envelope:		
Methylhydroxypropyl cellulose	5.00	5.00
Lactose	5.00	5.00
Ethyl cellulose	10.00	10.00
Macrogol	3.00	3.00
Titanium dioxide	<u>3.00</u>	<u>3.00</u>
Envelope total:	26.00	26.00
Film tablet total:	991.00	991.00

The granulate was produced and processed in a manner analogous to Example 1; the tableting proceeded in a corresponding manner without problems.

## Example 3

Hydrocolloid-forming agent: sodium carboxymethyl cellulose  
Residual moisture: 2.1%.

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<u>Components</u>	Tablet (mg)	Mass ready for tablet pressing (kg/1 million pieces)
Core:		
Metformin hydrochloride	850.00	850.00
Sodium carboxymethyl cellulose	80.00	80.00
Polyvidone	35.00	35.00
Magnesium stearate	<u>5.00</u>	<u>5.00</u>
Core total:	970.00	970.00
Film envelope:		
Methylhydroxypropyl cellulose	5.00	5.00
Ethyl cellulose	10.00	10.00
Macrogol	4.00	4.00
Titanium dioxide	<u>3.00</u>	<u>3.00</u>
Envelope total:	22.00	22.00
Film tablet total:	992.00	992.00

The granulate was produced and processed in a manner analogous to Example 1; the tableting proceeded in a corresponding manner without problems.

## Example 4

Hydrocolloid-forming agent: polyacrylic acid  
Residual moisture: 2.8%.

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<u>Components</u>	Tablet (mg)	Mass ready for tablet pressing (kg/1 million pieces)
Core:		
Metformin hydrochloride	850.00	850.00
Polyacrylic acid	60.00	60.00
Methylhydroxypropyl cellulose	30.00	30.00
Magnesium stearate	<u>5.00</u>	<u>5.00</u>
Core total:	945.00	945.00
Film envelope:		
Methylhydroxypropyl cellulose	10.00	10.00
Ethyl cellulose	10.00	10.00
Macrogol	3.00	3.00
Titanium dioxide	<u>3.00</u>	<u>3.00</u>
Envelope total:	26.00	26.00
Film tablet total:	971.00	971.00

The granulate was produced and processed in a manner analogous to Example 1, except that in this case methylhydroxypropyl cellulose served as a binder. The tableting proceeded without problems.

## Example 5

Hydrocolloid-forming agent: hydroxypropyl cellulose  
Residual moisture: 1.95%.



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<u>Components</u>	Tablet (mg)	Mass ready for tablet pressing (kg/1 million pieces)
Core:		
Metformin hydrochloride	850.00	850.00
Hydroxypropyl cellulose	60.00	60.00
Polyvidone	40.00	40.00
Magnesium stearate	<u>5.00</u>	<u>5.00</u>
Core total:	955.00	955.00
Film envelope:		
Poly(ethyl acrylate-methyl methacrylate) dispersion 30%	6.00*	6.00*
Talcum	1.20	1.20
Anti-foaming agent	<u>0.07</u>	<u>0.07</u>
Envelope total:	7.27	7.27
Film tablet total:	962.270	962.270

\*Stated quantity refers to the dry substance.

The granulate was produced and processed in a manner analogous to Example 1, except that in this case hydroxypropyl cellulose, the hydrocolloid-forming agent, was not granulated simultaneously but was dry-mixed with the completed granulate.

## Example 6

Hydrocolloid-forming agent: methylhydroxypropyl cellulose  
Residual moisture: 2.0%.

In the following example an additional binder was completely omitted, and the methylhydroxypropyl cellulose used assumed the function of both binder and retardant.

<u>Components</u>	Tablet (mg)	Mass ready for tablet pressing (kg/1 million pieces)
Core:		
Metformin hydrochloride	850.00	850.00
Methylhydroxypropyl cellulose	100.00	100.00
Magnesium stearate	<u>5.00</u>	<u>5.00</u>
Core total:	955.00	955.00
Film envelope:		
Methylhydroxypropyl cellulose	20.00	20.00
Ethyl cellulose	12.00	12.00
Macrogol	4.00	4.00
Titanium dioxide	<u>4.00</u>	<u>4.00</u>
Envelope total:	40.00	40.00
Film tablet total:	995.00	995.00

#### Production

The production of granulate was carried out in five partial batches. For each of the five partial batches, 170 kg of the active substance metformin hydrochloride and 18 kg methylhydroxypropyl cellulose were placed in a fluid bed granulator. 2 kg methylhydroxypropyl cellulose was dissolved in 50 L water. The dry mixture was granulated with the binder solution in the fluid bed granulator and then dried. The five partial batches were combined and admixed with 5 kg magnesium stearate. This mass ready for pressing was tableted. The tablet cores were coated in a coating pan with the film of the described composition.

#### Example 7

Hydrocolloid-forming agent: methylhydroxypropyl cellulose  
Residual moisture: 0.49%.

A moisture content of 0.49% was obtained in the mixture described below. The tableting had to be discontinued due to high losses caused by capping.

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<u>Components</u>	Tablet (mg)
Core:	
Metformin hydrochloride	850.00
Methylhydroxypropyl cellulose	40.00
Polyvidone	38.00
Magnesium stearate	<u>5.00</u>
Core total:	953.00 [sic]
Film envelope:	
Methylhydroxypropyl cellulose	20.00
Ethyl cellulose	12.00
Macrogol	4.00
Titanium dioxide	<u>4.00</u>
Envelope total:	40.00
Film tablet total:	993.00

## Example 8

Hydrocolloid-forming agent: gelatin

Residual moisture: 0.48%.

A moisture content of 0.48% was obtained in the mixture described below. The tableting had to be discontinued due to high losses caused by capping.

<u>Components</u>	(mg)
Core:	
Metformin hydrochloride	850.00
Lactose	70.00
Gelatin	40.00
Silicon dioxide, highly dispersed	2.00
Magnesium stearate	<u>2.50</u>
Core total:	964.50
Film envelope:	
Methylhydroxypropyl cellulose	10.00
Ethyl cellulose	9.00
Diethyl phthalate	3.00
Titanium dioxide	<u>3.00</u>
Envelope total:	25.00
Film tablet total:	989.5

## Claims

1. Pharmaceutical composition containing metformin as an active substance and a hydrocolloid-forming agent as a retardant, and, optionally, standard pharmaceutical auxiliary substances, the residual moisture content of the pharmaceutical composition being 0.5–3% by weight.
2. Pharmaceutical composition according to Claim 1, characterized in that the active substance content of metformin is at least 70%.
3. Pharmaceutical composition according to Claim 1 or 2, characterized in that the quantity of hydrocolloid-forming agent is 4–15% by weight.
4. Pharmaceutical composition according to one of Claims 1 through 3, characterized in that the hydrocolloid-forming agent is chosen from the group comprising cellulose derivatives, dextrans, starches, carbohydrate-based polymers, natural gums, xanthane, alginates, gelatin, polyacrylic acid, polyvinyl alcohol, and polyvinylpyrrolidone.
5. Pharmaceutical composition according to Claim 4, characterized in that the hydrocolloid-forming agent is a cellulose derivative, in particular an alkyl or hydroxyalkyl cellulose.
6. Pharmaceutical composition according to Claim 5, characterized in that the hydrocolloid-forming agent is chosen from methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, methylhydroxyethyl cellulose, methylhydroxypropyl cellulose, or sodium carboxymethyl cellulose.
7. Pharmaceutical composition according to one of Claims 1 through 6 containing 3–5% by weight binder, up to 2% by weight flow-regulating agent, and up to 2% by weight lubricant.
8. Pharmaceutical composition according to one of Claims 1 through 6 for the manufacture of pressed solid pharmaceutical forms of administration, in particular tablets or compacted products, for filling into capsules.
9. Pharmaceutical form of administration in the form of tablets or compacted products for filling into capsules, containing metformin as an active substance and a hydrocolloid-forming agent as a retardant, having a residual moisture content of 0.5–3% by weight relative to the weight of the tablet core or the capsule filling material.
10. Pharmaceutical form of administration according to Claim 9 in the form of a tablet having a final weight less than 1300 mg.
11. Method for the manufacture of pharmaceutical compositions containing metformin as an active substance and a hydrocolloid-forming agent as a retardant, and, optionally, standard pharmaceutical auxiliary substances, characterized in that the active substance and retardant, or a portion thereof, are granulated with an aqueous solvent optionally containing a binder, and the remaining portion of the retardant or additional standard pharmaceutical auxiliary substances is optionally mixed with the granulate, which is then dried until the residual moisture content is 0.5–3% by weight.
12. Method according to Claim 11, characterized in that the granulate is pressed into tablets which may then optionally be coated with a film envelope.
13. Method according to Claim 11, characterized in that the granulate is compacted and filled into capsules.
14. Method according to Claim 11, characterized in that methylhydroxypropyl cellulose is used as the hydrocolloid-forming agent.
15. Method according to Claim 11, characterized in that for the manufacture of the granulate up to 2% by weight flow-regulating agent, up to 2% by weight lubricant, and up to 5% by weight binder relative to the final pharmaceutical composition are used.
16. Use of pharmaceutical compositions according to one of Claims 1 through 8 for the manufacture of pressed pharmaceutical forms of administration, in particular tablets or compacted products, for filling into capsules.

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1 page of drawings is attached hereto.

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Figure 1

In-vitro active substance release of metformin, 850 mg delayed-release preparation

Time (min)

Released (%)

508 092/100